RESPONSE

A. Status of the Claims

Claims 18–49 were pending at the time of the Action. Claims 27–36, 40, and 44–49 were withdrawn as directed to nonelected subject matter. Claims 19, 20, 26, 41, and 42 are currently canceled. Claims 18, 37, and 43 are currently amended. Claims 44–47 and 49 were withdrawn and are currently amended. New claims 50–53 are added. No new matter was added by these amendments. Thus, the claims currently under examination are 18, 21–25, 37–39, 43, and 50–53.

B. Claim Objection

The Action objects to claim 19. In light of Applicants' cancellation of claim 19, the objection is moot.

C. Rejections Under 35 U.S.C. § 112

The Action rejects claims 18–20, 23–26, 37–39, and 41–43 under 35 U.S.C. § 112, first and second paragraphs. As discussed below, Applicants respectfully traverse those rejectsion.

1. The Indefiniteness Rejection

The Action rejects claim 26 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In light of Applicants' cancellation of claim 26, the rejection is moot.

2. The Enablement Rejections

The Action rejects claims 18–20, 23-26, 37–39, and 41–43 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Applicants traverse those rejections.

To meet the enablement requirement, the specification need only teach one skilled in the relevant art how to make and to use the invention, as defined by the claims, without the need to perform undue experimentation. *See* MPEP §2164. Here, the claims are directed to

polypeptides that have the following characteristics: (1) the polypeptides comprise an amino acid sequence having at least 90% amino acid identity with the amino acid sequence from amino acid residue 27 to amino acid residue 175 of SEQ ID NO:1; and (2) the polypeptides have anti-apoptotic activity. The Action alleges that the claims lack enablement because one would have to perform undue experimentation to identify the amino acid positions of the recited region of SEQ ID NO:1 that are tolerant to change. Applicants respectfully disagree.

One of skill in the art would readily know how to determine which amino acid residues are likely tolerant to change. The HIP/PAP protein is conserved across species and belongs to a family of structurally related proteins. Moreover, the distinct protein domains present in HIP/PAP have been identified and would be known to one of ordinary skill in the art. *See* Christa *et al.*, 1996, at G993, Abstract (271 AM. J. PHYSIOLOGY G993–1002, cited at page 14 of the Action). Thus, one of ordinary skill in the art could use protein alignment methods to analyze sequences of known HIP/PAP proteins and known structurally related proteins to determine which domains and residues are likely necessary to provide biological activity, as well as which domains and residues are likely tolerant to change. In fact, the specification provides explicit guidance regarding how to align proteins and describes tools known in the art for performing protein alignment. *See* Specification at page 11, line 31–page 12, line 12. Thus, the ordinarily skilled artisan could predict, without undue experimentation, whether a particular polypeptide comprising a sequence having 90% identity to the recited sequence would likely have the required biologic activity.

Moreover, one of ordinary skill in the art need not perform undue experimentation to determine if any particular polypeptide possesses the required anti-apoptotic activity. The specification explicitly teaches how to assess such activity and provides working examples

wherein the anti-apoptotic activity was determined. *See* Specification at page 32, line 26–page 33, line 11; page 38, line 21–page 39, line 13.

Finally, Applicants have submitted data that demonstrate that a polypeptide that meets the sequence limitation of the claim—*i.e.*, it comprises a sequence having 90% identity to amino acids 27–175 of SEQ ID NO:1—is likely to possess the required anti-apoptotic activity. As explained in the attached report entitled "Comparison of short versus full length ALF-5755 activity on primary culture of rat hepatocytes," which is attached as Appendix A, a polypeptide having 93.9% identity to amino acids 27–175 of SEQ ID NO:1 exhibited the same anti-apoptotic activity on cultured hepatocytes subjected to a combination of TNFa and actinomycin D as a polypeptide having almost 100% identity to amino acids 27–175 of SEQ ID NO:1. *See* Appendix A at Figure 1. Specifically, the report describes experiments that were performed to compare the anti-apoptotic activity of a polypeptide having amino acids 36–175 of HIP/PAP, called 36–175 HIP/PAP, to the biological activity of a polypeptide having amino acids Met-27–175 of HIP/PAP, called Met-27–175 HIP/PAP (*i.e.*, a polypeptide having an additional N-terminal methionine residue as compared to 27–175 HIP/PAP).

To study the anti-apoptotic activity of the HIP/PAP polypeptides (also called ALF-5755 in the report), a caspase 3 inhibition test was performed to evaluate the ability of the HIP/PAP polypeptides to inhibit apoptosis in rat hepatocytes in primary culture after the hepatocytes had been stimulated to undergo apopotosis. *See* Appendix A at pages 3 (I) and 5 (4). The results showed that the anti-apoptotic activity of 36–175 HIP/PAP was as high as that of Met-27–175 HIP/PAP in rat hepatocyte primary cultures. *See* Appendix A at pages 5–6 (III) and Figure 1. The IC_{50} values for the two proteins were comparable (264 and 238 ng/mL, respectively) with widely overlapping intervals of confidence (175–399 and 139–410 ng/mL respectively). *See* Appendix A at pages 5–6. Thus, 36–175 HIP/PAP, a polypeptide having 93.9% identity to

amino acids 27–175 of HIP/PAP, exhibited the same anti-apoptotic activity as a polypeptide having almost 100% identity to amino acids 27–175 of HIP/PAP (*i.e.*, Met-27–175 HIP/PAP, which has 99.3% identity to amino acids 27–175 of HIP/PAP). In other words, the deletion of 10 amino acids of the Met-27–175 HIP/PAP form that provides the 36–175 HIP/PAP results in ***no change*** in the biological activity of the protein. Applicants are also in the process of collecting additional data, which may be the subject of an additional submission in this matter.

In summary, Applicants' claims are enabled for at least the following reasons. First, the present application includes various examples to illustrate the biological activity, and more precisely, the anti-apoptotic activity of a HIP/PAP polypeptide (see Example 4). It is noted that one skilled in the art would know, particularly based on the reference to the Christa *et al.* publication at page 34, line 8 of the specification, that the said exemplified polypeptide, which is a 16 kDa form of HIP/PAP, refers to the amino acids 27–175 of SEQ ID NO:1 resulting from the cleavage of the 26-amino acid peptide signal. *See* Christa *et al.*, *High Expression of the Human Hepatocarcinoma-Intestine-Pancreas/Pancreatic-Associated Protein (HIP/PAP) Gene in the Mammary Gland of Lactating Transgenic Mice*, 267 EUR. J. BIOCHEM. 1665–71 (2000), at page 1667, 2nd column (attached as Appendix B).[1]

Second, the additional experimental data submitted herewith demonstrate that a polypeptide having 93.9% identity to the recited sequence has the same anti-apoptotic activity as a polypeptide having almost 100% identity to the recited sequence. Thus, one of ordinary skill in the art would understand that a polypeptide comprising an amino acid sequence that has 90% identity to the recited portion of SEQ ID NO:1 would likely retain anti-apoptotic activity, as

[1] The Action acknowledges, at page 15, that the mature 16 kDa human HIP/HAP, as used in the examples, contains residues 26–175 of SEQ ID NO:1.

required by the claims. Moreover, as discussed above, one of ordinary skill in the art could predict, without undue experimentation, whether a particular polypeptide having 90% identity to the recited sequences would likely have the required anti-apoptotic activity. Finally, one of ordinary skill in the art need not perform undue experimentation to determine if any particular polypeptide possesses the required anti-apoptotic activity, particularly in light of the fact that the specification expressly teaches how to assay anti-apoptotic activity. For at least these reasons, the specification contains a description sufficient to enable one skilled in the art to make and use the claimed invention without unduly extensive experimentation. The claims, therefore, are enabled.

Claims 50–53 are enabled for additional reasons. Namely, claims 50–53 are enabled for the same reasons that claim 21—which was not included in the enablement rejection—is enabled. Claim 21 is directed to a polypeptide that comprises the amino acid sequence from amino acid residue 27 to amino acid residue 175 of SEQ ID NO:1. Applicants provided working examples demonstrating that such a polypeptide has anti-apoptotic activity. *See, e.g.*, Specification at Example 4. For the same reasons that claim 21 is enabled, claims 50–53 are likewise enabled. Claims 50 and 51 are directed to polypeptides consisting essentially of or consisting of amino acids 27–175 of SEQ ID NO:1. Claims 52 and 53 are directed to polypeptides consisting essentially of or consisting of polypeptides having at least 90% identity to amino acids 27–175 of SEQ ID NO:1. Because the specification shows that amino acids 27–175 of SEQ ID NO:1 possess the required anti-apoptotic activity, and because Applicants have submitted experimental data demonstrating that a polypeptide having 93.9% identity to amino acids 27–175 of SEQ ID NO:1 also has the required anti-apoptotic activity, claims 50–53 are enabled.

3. The Written Description Rejections

The Action rejects claims 18–20, 23–26, 37–39, and 41–43 under 35 U.S.C. § 112, second paragraph, as allegedly lacking written description. Applicants respectfully traverse those rejections.

To meet the written description requirement, Applicants need only "reasonably convey[] to the artisan that the inventor had possession at that time of the later claimed subject matter." MPEP § 2163.02 (quoting *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985)). Here, the description reasonably conveys possession of the invention. The claims are directed to polypeptides comprising an amino acid sequence having at least 90% identity to amino acids 27–175 of SEQ ID NO:1. The specification provides literal written description support for that invention. *See, e.g.*, Specification at page 13, lines 24–29 ("Another object of the invention is a pharmaceutical composition for stimulating liver regeneration *in vivo* comprising an effective amount of a polypeptide comprising an amino acid sequence having 90% amino acid identity with the polypeptide consisting of the amino acid sequence starting at the amino acid residue 27 and ending at the amino acid residue 175 of sequence SEQ ID NO:1, in combination with at least one physiologically acceptable excipient."); Specification at page 12, line 33–page 13, line 2 ("According to the invention a first amino acid sequence having at least 90% of identity with a second amino acid sequence, comprises at least 90 %, and preferably at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of identity in amino acids with said second amino acid sequence."). Thus, while the examples regard a polypeptide having amino acids 27–175 of SEQ ID NO:1, the specification makes clear that the invention is broader than the working examples provided. It appears the Action is improperly attempting to limit Applicants' claims to a preferred embodiment even though the specification's disclosure explicitly states a broader application. The law is clear that Applicants need not

provide working examples for all polypeptides encompassed by the claims because "examples are not necessary to support the adequacy of a written description." *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 1992).

The Action further reasons that the claims lack written description because one of skill in the art would not, based on the specification, be able to predictably identify the polypeptides encompassed by the claims. *See* Action at page 13. Applicants respectfully disagree. The specification discloses that a polypeptide comprising amino acids 27–175 of SEQ ID NO:1 has anti-apoptotic activity. Further, as explained above, one of ordinary skill in the art would have known, based on the specification, how to identify additional polypeptides that meet the claim limitations. Thus, the ordinarily skilled artisan reading the specification at the time of filing would have understood that Applicants were in possession of polypeptides comprising an amino acid sequence having at least 90% identity to amino acids 27–175 of SEQ ID NO:1.

In view of the above, the present specification describes the claimed invention in sufficient detail that one of ordinary skill in the art could reasonably conclude at the time of filing that Applicants had possession of the claimed invention. Applicants thus respectfully request withdrawal of the rejections.

Moreover, claims 50–53 meet the written description requirement for additional reasons. As the Action acknowledges, claim 21 is adequately described. For the same reasons, claims 50–53 also meet the written description requirement. Claim 21 is directed to a polypeptide that comprises an amino acid sequence from amino acid residue 27 to amino acid residue 175 of SEQ ID NO:1. Applicants have provided the structure of such a polypeptide by providing SEQ ID NO:1. Like claim 21, claims 50 and 51—which are directed to polypeptides consisting essentially of or consisting of amino acids 27–175 of SEQ ID NO:1—likewise meet the written description requirement because Applicants have described the structure of such a polypeptide

by providing SEQ ID NO:1. Similarly, claims 52 and 53—which are directed to polypeptides consisting essentially of or consisting of polypeptides having at least 90% identity to amino acids 27–175 of SEQ ID NO:1—are sufficiently described based on the description of SEQ ID NO:1 and in light of the fact that one of ordinary skill in the art would have known, based on the specification, how to identify any additional polypeptides that meet the claim limitations.

D. Rejections Under 35 U.S.C. § 102

The Action rejects claims 18–25, 37–39, 41, and 43 under 35 U.S.C. § 102 as allegedly anticipated by Christa *et al.*, 1996 ("Christa (1996)"). Action at page 14. Applicants traverse those rejections.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP § 2131 (quoting *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). Here, the claims are directed to pharmaceutical compositions that include at least one physiologically acceptable excipient. Thus, the claims are not anticipated by Christa (1996) unless that reference discloses the required at least one physiologically acceptable excipient.

As explained in Applicants' specification:

> For the purpose of the present invention, HIP/PAP can be formulated according to known methods to prepare pharmaceutical useful compositions, whereby HIP/PAP is combined in admixture with a pharmaceutical acceptable carrier. Suitable carriers and their formulations are described in Remington's Pharmaceutical Science, 16th ed;, 1980, Mack publishing Co, edited by Oslo et al. By <<physiologically acceptable excipient>> is meant solid or liquid filler, diluent or substance, ***which may be safely used in systemic or topical administration***.

Specification at page 20, lines 3–11 (emphasis added). The Action alleges that Christa (1996) discloses a physiologically acceptable excipient by describing acetic acid buffer and milk from

transgenic mice. Applicants respectfully disagree. Nothing in Christa (1996) indicates that the disclosed acetic acid buffer or milk from transgenic mice could be safely used in systemic or topical administration. Thus, the claims are not anticipated because Christa (1996) does not teach the required physiologically acceptable excipient.

Further, Applicants submit that claims 18–25 and 43 are directed to pharmaceutical compositions, as explicitly stated in the preamble. Applicants respectfully disagree with the Action's position that the recitation of "pharmaceutical composition" in the claim is "an intended use and bears no accorded patentable weight to distinguish a claimed product over one from the prior art." Action at 14. To the contrary, "[d]uring examination, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference . . . between the claimed invention and the prior art." MPEP § 2111.02(II). Here, one of skill in this art would understand, based on the specification, that use as a pharmaceutical composition results in structural differences between the claimed invention and the cited prior art. For example, the specification teaches:

> In a first preferred embodiment, the pharmaceutical composition of the invention comprises a biologically active portion of HIP/PAP as described hereabove, which can be isolated from cell or tissue sources by an appropriate purification scheme using standard protein purification techniques.

Specification at page 11, lines 16–26. Thus, the specification teaches that the claimed pharmaceutical compositions comprise a polypeptide that is purified.

Further, one of ordinary skill in the art would have understood that when a pharmaceutical composition comprises a polypeptide as an active ingredient, the polypeptide used as an active ingredient must consist of a polypeptide purified according to pharmaceutical requirements. Indeed, the qualification of a composition as a pharmaceutical composition, and

specifically the qualification of a protein-containing composition as a pharmaceutical composition, involves numerous safety and therapeutic activity requirements.

Namely, a composition qualifies as a pharmaceutical composition when the qualitative and quantitative constitution of the composition's active ingredient(s) and excipient(s) comply with generally accepted requirements. Regarding protein-containing pharmaceutical compositions, one of skill in the art would know that emphasis is placed on the purity requirements relating to the protein active ingredient. Such protein purity requirements may be found in the guidelines drafted by national or regional Drug Agencies, such as the FDA (Food and Drug Administration) and the EMEA (European Agency for the Evaluation of Medicinal Products). For example, one can refer to any of the following: *see, e.g., Guidance for Industry*, U.S. Dept. of Health and Human Services, August 1999, at page 12 (attached as Appendix C) (explaining that procedures for evaluating a drug substance "should focus on the separation of the desired product from product-related substances and from impurities"); *Guidance for Industry*, Center for Biologics Evaluation and Research, August 1996, at page 16, F.2. (attached as Appendix D) (requiring documentation of impurities in a protein drug substance); *Points to Consider in the Production and Testing of New Drugs and Biologics, Draft*, Office of Biologics Research and Review, April 1985, at pages 9 and 11 (attached as Appendix E) (discussing the required protein purification and methods for assessing purity); *Quality of Biotechnological Products*, Int'l Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, July 1996, at page 6 (attached as Appendix F) (requiring documentation of purity); *Quality of Biotechnological Products*, European Agency for the Evaluation of Medicinal Products (EMEA), December 1995, at page 273 (attached as Appendix G) (defining impurity as "[a]ny component of the active substance (bulk material) or medicinal product (final container product) which is not the chemical entity defined as the active substance,

an excipient, or other additives to the medicinal product"); *Production and Quality Control of Medicinal Products Derived by Recombinant DNA Technology*, EMEA, July 1995, at page 214 (attached as Appendix H) ("The residual cellular proteins should also be determined by an assay with appropriate sensitivity (e.g. ppm) and strict upper limits set."); *Use of Transgenic Animals in the Manufacture of Biological Medicinal Products for Human Use*, EMEA, July 1995, at page 293 (attached as Appendix I) ("The source material, whether blood, milk, colostrum or other tissue will contain large numbers of host derived proteins other than the desired product").

It flows from the preceding remarks that for a protein-containing composition to qualify as a protein-containing ***pharmaceutical*** composition, various basic requirements must be met, which include: (a) that the composition does not comprise a component which is not a chemical entity defined as an active substance, an excipient, or other additives to the medicinal product; and (b) that the composition notably does not comprise residual cellular proteins and more generally process-related impurities (*e.g.*, host cell proteins or DNA) and product-related impurities (*e.g.*, protein precursors, protein degradation products, etc.). Specifically, when dealing with protein active ingredients originating from transgenic animals and in particular from transgenic animal milk, the said protein-containing composition must not contain host-derived proteins other than the desired product or other host fluids because such host proteins or fluids are likely to be immunogenic or carry infectious agents.

Notably, the HIP/PAP proteins (namely recombinant HIP/PAP from *E. Coli* or from transgenic mice milk) described in Christa (1996) are not pure, as can be seen by the appearance of additional protein entities in the gel pictured in Fig. 2. The transgenic HIP/PAP preparations described by Christa (1996) consist of "HIP-PAP-enriched preparations" and not highly purified HIP/PAP preparations. Indeed, the fact that Christa (1996) does not disclose purified HIP/PAP is not surprising, considering that Christa (1996) does not discuss administration of HIP/PAP and

mentions neither pharmaceutical compositions comprising a HIP/PAP polypeptide nor the pharmaceutical interest of HIP/PAP polypeptides. In contrast, Applicants' claims are directed to pharmaceutical compositions. Illustratively, Applicants enclose a report from the French Research and Education Evaluation Agency ("AERES") dated December 2008, which discusses the usefulness of Met-27–175 HIP/PAP ("ALF-5755") in the treatment of liver disease—specifically, fulminant liver failure—and gave the clinical project an "A" grade. *See Evaluation Report*, AERES, December 2008, at pages 7–8 (attached as Appendix J). Thus, claims 18–25 and 43 are novel over the Christa (1996) reference because the reference does not teach a pharmaceutical composition, as required by the claims.

For the foregoing reasons, Applicants respectfully request withdrawal of the anticipation rejections.

E. Rejections Under 35 U.S.C. § 103

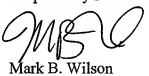
Claim 42 was rejected under 35 U.S.C. § 103 as allegedly obvious over Christa (1996) in view of Tanaka *et al.* In light of Applicants' cancellation of claim 42, the rejection is moot.

F. Conclusion

Applicants believe that they have submitted a complete reply to the Office Action dated February 18, 2010, and respectfully request favorable consideration of the claims in view of the amendments and statements contained herein.

Should the Examiner have any questions, comments, or suggestions relating to this case, the Examiner is invited to contact the undersigned Applicants' representative at (512) 536-3035.

Respectfully submitted,



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